JCI The Journal of Clinical Investigation

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J Clin Invest. 1975;55(2):218-223. https://doi.org/10.1172/JCI107924.

Research Article

To determine if propylthiouracil (PTU) inhibited extrathyroidal thyroxine (T4) to triiodothyronine (T3) conversion in man, PTU was administered to T4-treated hypothyroid patients and serial measurements of T4, T3, and thyrotropin (TSH) carried out. All patients had proven thyroidal hypothyroidism and had been receiving 0.1 or 0.2 mg T4 daily for at least 2 mo before study. Hormone measurements were made for 5 consecutive days before and daily during a 7-day treatment period with PTU, 1,000 mg/day. In eight patients receiving 0.1 mg T4 daily, administration of PTU resulted in a prompt fall in mean serum T3 concentrations from 78 plus or minus 6 ng/100 ml (SEM) to 61 plus or minus 3 ng/100 ml after 1 day. The mean serum T3 concentrations ranged from 55 to 60 ng/100 ml during the remainder of the PTU treatment period (P less than 0.01). The mean control serum TSH concentration was 29.6 muU/ml and it increased to a peak of 40 muU/ml on the 5th and 6th days. In five patients receiving 0.2 mg T4 daily, the mean control serum T3 concentration was 84 plus or minus 7 NG/100ML. It fell to 70 plus or minus 5 ng/100 ml after 1 day and 63 plus or minus 7 ng/100 ml after 2 days of PTU administration and thereafter ranged from 6) to 69 […]

Reduction in Extrathyroidal Triiodothyronine Production by Propylthiouracil in Man

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ABSTRACT To determine if propylthiouracil (PTU) inhibited extrathyroidal thyroxine (T_4) to triiodothyronine (T_3) conversion in man, PTU was administered to T_4-treated hypothyroid patients and serial measurements of T_4, T_3, and thyrotropin (TSH) carried out. All patients had proven thyroidal hypothyroidism and had been receiving 0.1 or 0.2 mg T_4 daily for at least 2 mo before study. Hormone measurements were made for 5 consecutive days before and daily during a 7-day treatment period with PTU, 1,000 mg/day.

In eight patients receiving 0.1 mg T_4 daily, administration of PTU resulted in a prompt fall in mean serum T_3 concentrations from 78±6 ng/100 ml (SEM) to 61±3 ng/100 ml after 1 day. The mean serum T_3 concentrations ranged from 55 to 60 ng/100 ml during the remainder of the PTU treatment period ($P < 0.01$): The mean control serum TSH concentration was 29.6 μU/ml and it increased to a peak of 40 μU/ml on the 5th and 6th days. In five patients receiving 0.2 mg T_4 daily, the mean control serum T_3 concentration was 84±7 ng/100 ml. It fell to 70±5 ng/100 ml after 1 day and 63±7 ng/100 ml after 2 days of PTU administration and thereafter ranged from 61 to 69 ng/100 ml ($P < 0.01$). Serum TSH concentrations did not increase. No changes in serum T_4 concentrations were found in either group. In five patients who received 100 mg methimazole (MMI) daily for 7 days there were no changes in serum T_4, T_3, or TSH concentrations.

These results indicate that PTU, but not MMI, produces a prompt and sustained, albeit modest, reduction in serum T_3 concentrations in patients whose sole or major source of T_3 is ingested T_4. These findings most likely result from inhibition of extrathyroidal formation of T_3 from T_4.

Received for publication 4 June 1974 and in revised form 9 September 1974.

INTRODUCTION

Propylthiouracil (PTU)[1] has been shown to have both intra- and extrathyroidal antithyroid actions. It inhibits many of the peripheral actions of thyroxine (T_4) and slows the peripheral deiodination and, in some studies, the overall rate of degradation of T_4 in both animals and man (1–6). In contrast, while PTU has been shown to slow the fractional deiodination and degradation rate of triiodothyronine (T_3) in animals (2, 6, 7), it has not been found to inhibit the biological actions of T_3 (1). It is now clear that an important pathway of extrathyroidal T_4 metabolism is conversion of T_4 to T_3, a more potent thyroid hormone, and that a large portion of the serum T_3 is produced as a result of extrathyroidal conversion from T_4 (8–10). Thus, the extrathyroidal antithyroid actions of PTU might reflect reduction in serum T_3 concentrations due to inhibition of peripheral T_4 deiodination. It has previously been shown by Oppenheimer, Schwartz, and Surks that PTU inhibited the rate of conversion of [^{125}I]T_4 to [^{125}I]T_3 in rats (7).

The present study was undertaken to determine if PTU could be shown to inhibit extrathyroidal T_3 formation in man. To obviate alterations in thyroidal T_4 or T_3 secretion occurring as a result of PTU treatment, patients with documented hypothyroidism receiving chronic T_4 therapy were studied. The results indicate that administration of PTU, but not methimazole (MMI), results in significant reduction in serum T_3 concentrations in T_4-treated hypothyroid patients. Similar results have been presented in abstract form by Geffner, Azukizawa, and Hershman (11).

[1] *Abbreviations used in this paper:* MMI, methimazole; PTU, propylthiouracil; TSH, thyrotropin; T_3, triiodothyronine; T_4, thyroxine.

METHODS

Study subjects. 10 patients, 8 women and 2 men, with thyroidal hypothyroidism were studied. Their ages ranged from 21 to 76 yr. In all, hypothyroidism had been documented by the presence of typical manifestations and appropriate laboratory abnormalities. The hypothyroidism was idiopathic in four, was due to Hashimoto's thyroiditis in four, was because of [^{131}I]iodide therapy in one, and followed thyroidectomy for thyroid carcinoma in one. In these patients, pretreatment serum T_4 concentrations ranged from 0.8 to 5.1 μg/100 ml, pretreatment serum T_3 concentrations ranged from < 30 to 74 ng/100 ml and pretreatment serum thyrotropin (TSH) concentrations ranged from 11.9 to 268 μU/ml. None had any evidence of other endocrine or significant systematic disease, and none were taking medications other than T_4 at the time of the PTU and MMI studies. Each patient was informed of the nature of the study and written consent was obtained at the time of each admission to the Clinical Research Center.

Experimental protocol. Each patient received T_4 in doses of 0.1 or 0.2 mg daily for at least 2 mo before antithyroid drug administration as well as daily throughout the study. Three groups of patients were studied. Group I consisted of eight patients receiving 0.1 mg T_4 daily who were treated with PTU. Group II consisted of five patients receiving 0.2 mg T_4 daily who were treated with PTU. Group III consisted of five patients receiving 0.1 mg T_4 daily who were treated with MMI.

At the time of each Clinical Research Center admission, measurements of thyroidal ^{131}I uptake at 2 and 24 h were obtained. This was done to ensure that the patients had little endogenous thyroid function, since several patients had elevations in serum TSH levels at the time of study. In all instances, with one exception, the 2- and 24-h thyroidal uptake values were 5% or less of the administered dose. The exception was a patient with Hashimoto's thyroiditis whose uptake was 11% at 2 h and 15% at 24 h while receiving 0.1 mg T_4 daily before receiving MMI.

Serum for T_4, T_3, and TSH determinations were collected 9 a.m. daily immediately before the daily T_4 dose was administered. The means of the five base-line serum T_4, T_3, and TSH measurements and the thyroidal ^{131}I uptake results in the patients in each group are shown in Table I. Starting on the 5th day, daily administration of either 1,000 mg PTU or 100 mg MMI in divided doses every 6 h was initiated and continued for 7 days. A final serum sample was obtained 1 day after PTU or MMI was discontinued. During antithyroid drug treatment, each patient was carefully observed and daily determinations of white blood cell and differential counts made. No significant changes in blood counts occurred.

Hormone analyses. Serum T_4 was measured by competitive protein-binding analysis (12). Serum T_3 and TSH were measured by radioimmunoassay (13, 14). Normal ranges for these hormones in this laboratory are; T_4, 5–11 μg/100 ml; T_3, 70–150 ng/100 ml; and TSH, < 1.5–8 μU/ml. All samples for determinations of either T_4, T_3, or TSH from any one subject were analyzed in the same assay. At the time that this study was done, intraassay variation for the three hormones was reevaluated by analysis of six to eight samples of varying hormone concentration. The following coefficients of variation were found, T_4, 5.3%; T_3, 4.4%; TSH, 12.4%.

Statistical analysis. The results obtained before and during antithyroid drug administration were analyzed by analysis of variance and calculations of the F ratio (15).

TABLE I

Individual Mean Control Serum T_4, T_3, and TSH Concentrations and Thyroidal ^{131}I Uptake Results at the Time of Antithyroid Drug Administration

	T_4*	T_3*	TSH*	^{131}I Uptake	
	μg/100 ml	*ng/100 ml*	*μU/ml*	*2 h*	*24 h*
Group I: 0.1 mg T_4, 1,000 mg PTU					
F. B.	6.8	80	22.0	3	5
E. C.	5.8	76	3.2	2	2
E. C. H.	6.6	72	37.3	3	5
W. D.	3.4	67	80.2	4	5
S. E.	7.6	67	9.9	3	1
K. M.	7.6	110	3.4	3	<1
A. O.	4.9	55	78.8	2	2
C. P.	8.3	96	2.0	2	<1
Group II: 0.2 mg T_4, 1,000 mg PTU					
F. B.	10.0	110	3.9	3	5
E. C. H.	7.0	91	26.2	2	<1
S. E.	8.7	71	2.1	3	2
C. P.	10.6	69	2.5	2	1
J. V.	7.6	81	3.9	4	4
Group III: 0.1 mg T_4, 100 mg MMI					
F. B.	7.1	64	23.5	3	5
E. C.	5.8	60	6.6	2	2
E. C. H.	5.6	79	70.8	2	<1
W. D.	5.6	70	60.1	4	5
M. T.	7.1	115	40.5	11	15

* Mean of 5 control days.

RESULTS

The results of serum T_4, T_3, and TSH concentrations before and during PTU administration to the eight patients receiving 0.1 mg T_4 are shown in Fig. 1. During the control period, the mean serum T_4 concentrations ranged from 6.1 to 6.5 μg/100 ml, the mean serum T_3 concentrations ranged from 73 to 83 ng/100 ml and the mean serum TSH concentrations ranged from 27 to 32 μU/ml. During PTU administration, mean serum T_4 concentrations did not change. In contrast, serum T_3 concentrations decreased abruptly in all patients. The mean control and lowest serum T_3 concentration in each patient is shown in Table II. The mean serum T_3 concentration was 61 ng/100 ml after 1 day and ranged from 55 to 60 ng/100 ml during subsequent days of PTU administration (Fig. 1). The serum T_3 concentrations during PTU administration were statistically significantly ($P < 0.01$) lower than control. The serum T_3 concentrations during PTU were not different from one another, however, indicating that the fall was not a progressive one. The mean serum T_3 concentration increased to 78 ng/100 ml 1 day after discontinuation of PTU. During PTU administration, the mean serum

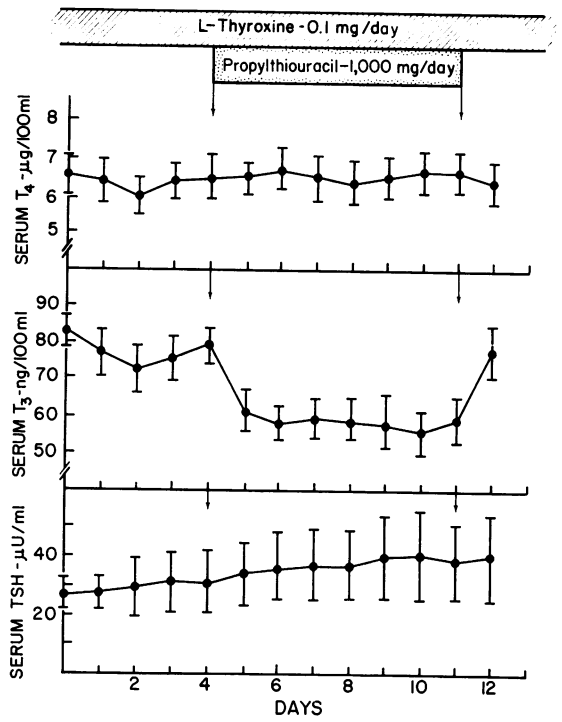

FIGURE 1 Mean serum T_4, T_3, and TSH concentrations in eight hypothyroid patients receiving 0.1 mg T_4 daily before and during PTU administration. The vertical bars indicate ±1 SEM.

TSH concentrations gradually increased but the changes were not statistically significant for the group as a whole (Table II) or when the values from patients with elevated and those with normal serum TSH concentrations were separately analyzed.

The results of PTU administration to five patients receiving 0.2 mg T_4 daily are shown in Fig. 2 and Table II. During the control period, the mean serum T_4 concentrations ranged from 8.6 to 9.0 µg/100 ml, the mean serum T_3 concentrations ranged from 82 to 88 ng/100 ml and the mean serum TSH concentrations ranged from 7.3 to 8.3 µU/ml. During PTU administration, mean serum T_4 concentrations did not change. The mean serum T_3 concentration fell to 70 ng/100 ml after 1 day of PTU administration. It was 63 ng/100 ml after 2 days and varied from 61 to 69 ng/100 ml on subsequent days. The fall in serum T_3 concentrations was statistically significant ($P < 0.01$). The mean serum T_3 concentration was 103 ng/100 ml 1 day after discontinuation of PTU. This value was significantly greater than control ($P < 0.01$). During PTU administration, mean serum TSH concentrations ranged from 7.8 to 10.2 µU/ml and were not significantly different from control.

The results of administration of MMI to five patients receiving 0.1 mg T_4 daily are shown in Fig. 3. During the control period, the mean serum T_4 concentrations ranged from 5.9 to 6.4 µg/100 ml, the mean serum T_3

TABLE II

Daily Serum TSH and Minimum Serum T_3 Concentrations in Patients Receiving PTU

	Serum TSH during PTU‡								
	Control*	5	6	7	8	9	10	11	Control*	Minimum
	µU/ml				µU/ml				ng/100 ml	
Group I: 0.1 mg T_4, 1,000 mg PTU										
W. D.	80.2	81.0	95.0	80.0	78.0	78.0	64.0	64.0	67	50
A. O.	78.8	80.0	76.0	81.0	80.0	120.0	141.5	118.5	55	36
E. C. H.	37.3	67.5	67.5	82.5	87.0	61.5	50.5	63.5	72	50
F. B.	21.8	26.2	28.4	26.4	24.8	31.0	33.5	26.1	80	61
S. E.	9.9	9.8	12.9	19.5	16.0	16.5	14.0	18.5	67	43
E. C.	3.2	3.1	4.1	5.6	4.1	6.0	8.4	7.0	76	52
K. M.	3.4	4.2	8.2	5.0	5.2	7.2	7.1	5.1	110	64
C. P.	2.0	1.8	1.6	1.5	1.5	1.8	1.8	2.5	96	44
Mean	29.6	34.2	36.7	37.7	37.1	40.2	40.2	38.1		
Group II: 0.2 mg T_4, 1,000 mg PTU										
E. C. H.	26.2	32.5	37.5	32.5	33.0	32.5	28.5	30.0	91	74
F. B.	3.9	3.0	3.5	3.4	3.7	3.4	3.0	4.2	110	70
J. V.	3.9	4.1	5.0	5.3	5.0	4.2	4.4	4.3	81	56
C. P.	2.5	2.0	3.2	3.0	3.0	2.0	2.6	1.9	69	53
S. E.	2.1	2.0	1.9	1.8	2.2	2.3	3.9	4.0	71	36
Mean	7.7	8.7	10.2	9.2	10.2	8.9	7.9	8.9		

* Mean of 5 control days.

‡ Treatment days (days 5–11) of study.

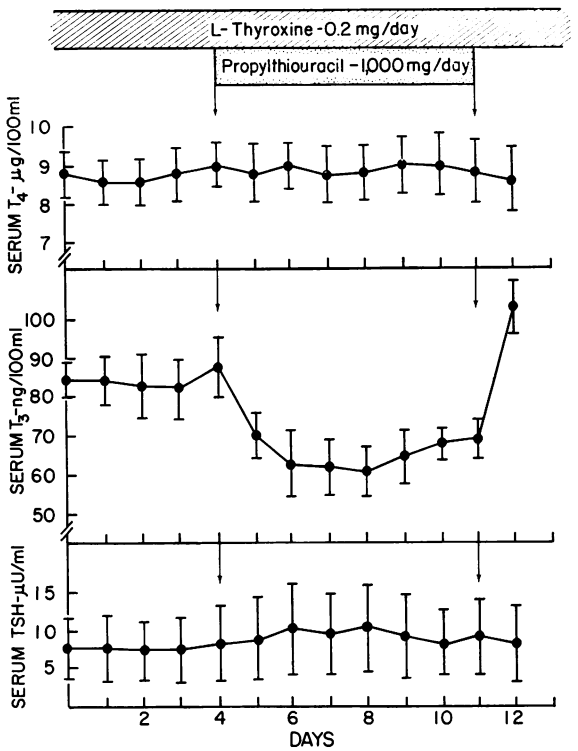

FIGURE 2 Mean serum T_4, T_3, and TSH concentrations in five hypothyroid patients receiving 0.2 mg T_4 daily before and during PTU administration. The vertical bars indicate ±1 SEM.

concentrations ranged from 76 to 78 ng/100 ml and the mean serum TSH concentrations ranged from 37.4 to 42.6 μU/ml. During MMI administration, the mean daily serum T_4 concentrations ranged from 5.7 to 5.9 μg/100 ml, the mean serum T_3 concentrations ranged from 70 to 77 ng/100 ml and the mean serum TSH concentration ranged from 37.0 to 52.5 μU/ml. None of these values nor those found 1 day after discontinuation of MMI were significantly different from control.

DISCUSSION

The results of this study clearly show that administration of PTU, but not MMI, results in decreased serum T_3 concentrations in patients whose major, if not sole, source of T_3 is orally administered T_4. The change in serum T_3 concentrations occurred within 24 h after initiation of the PTU and persisted throughout the period of PTU administration. The fall in serum T_3 concentrations was about 25% in both groups. There was a tendency for the serum TSH concentrations to increase in the patients receiving 0.1 mg T_4 daily, but the increase did not reach statistical significance probably due to the wide variation in serum TSH concentrations in these patients. The failure of serum TSH concentrations to increase at all during PTU administration in the patients receiving 0.2 mg T_4 daily is presumably because their serum TSH levels were lower, being well within the normal range in four of the five subjects in this group. Several studies of TSH-thyroid hormone interactions have suggested that small changes in serum thyroid hormone concentrations are associated with greater changes in serum TSH concentrations when the serum thyroid hormone concentrations are low than when they are normal (16, 17). Serum T_3 concentrations increased to control levels within 24 h after discontinuation of PTU in the patients receiving 0.1 mg T_4 daily and to a value significantly greater than control in the patients receiving 0.2 mg T_4 daily. The reason for the increase to above control in the latter group is not known. Unfortunately later samples were not obtained from these subjects. The rapidity of the changes in serum T_3 concentrations coincident with administration and withdrawal of PTU are similar to results reported by Nicoloff in studies of the effect of PTU on [^{131}I]T_4 deiodination in vivo (5), though in that study PTU was given for only 10 h at most.

The failure of serum T_4 concentrations to increase during PTU administration, as might have been expected, deserves brief comment. Data available from studies of labeled T_4 disappearance during PTU administration in humans have for the most part shown that

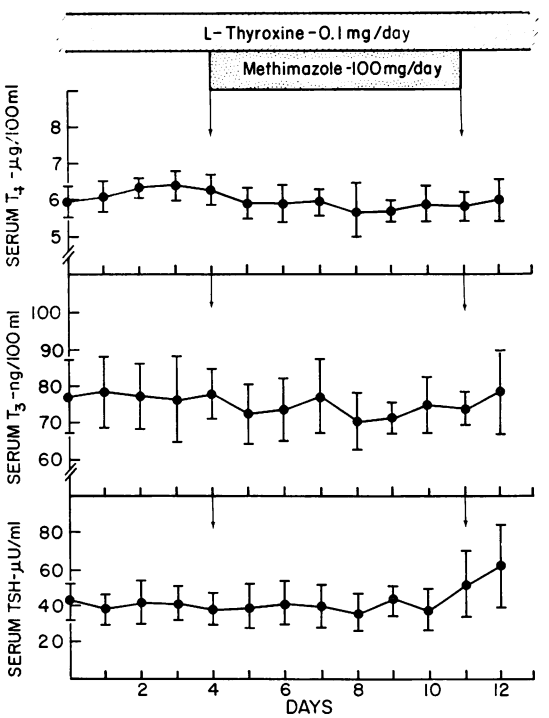

FIGURE 3 Mean serum T_4, T_3, and TSH concentrations in five hypothyroid patients receiving 0.1 mg T_4 daily before and during MMI administration. The vertical bars indicate ±1 SEM.

the overall rate of T_4 degradation is not changed by PTU administration (3, 4). The decrease in T_4 deiodination, usually measured as a decrease in urinary radioiodide excretion, has been found to be compensated by an increase in biliary and/or fecal radioiodide excretion (3). Even if this were not the case, the fall in serum T_3 concentrations found in this study was sufficiently small that it is unlikely that the quantity of T_4 not being converted to T_3 would result in measurable alterations in serum T_4 concentrations.

The results were clearly different in the patients who received MMI in the dosage used in that no changes in serum T_3 or TSH concentrations were found. The dosage used was chosen because its thyroidal action is comparable to that of 1,000 mg PTU. The lack of change during MMI was not unexpected since several studies have shown that MMI had no effect on T_4 action or degradation in animals and no effect on T_4 turnover in man (1, 18). However, it is possible that different doses of MMI might have some extrathyroidal action.

It seems reasonable to conclude that the decrease in serum T_3 concentrations occurred as a result of inhibition by PTU of the peripheral deiodination of T_4. This conclusion is supported by the slowing of T_4 deiodination produced by PTU in man (5). It also provides an explanation for the inhibition by PTU of the peripheral actions of T_4 on oxygen consumption, various tissue enzyme activities and TSH secretion observed in animals (1). Finally, the finding of reduced T_3 concentrations extends the finding of Oppenheimer and co-workers that PTU inhibited conversion of isotopically labeled T_4 to T_3 (7). An alternative interpretation that might be proposed to explain the present findings of decreased serum T_3 concentrations is that PTU accelerates T_3 degradation without altering extrathyroidal T_3 production. The effect of PTU on T_3 turnover in man has not been studied. However, acceleration of T_3 turnover in man seems unlikely in view of the reports that PTU slows the fractional turnover rate of T_3 in animals (2, 6) and that PTU does not inhibit the peripheral effects of T_3 (1). It is also possible that PTU might decrease serum T_3 concentrations by inhibiting T_3 binding to thyroid hormone-binding proteins. However, several studies have shown that PTU does not alter binding of labeled T_3 or T_4 to plasma proteins or alter serum thyroxine-binding-globulin-binding capacity (19, 20). Studies in this laboratory have shown that PTU (10 mg/ml) or MMI (1 mg/ml) added in vitro to serum did not alter its measured T_3 concentration (unpublished observations).

There are several potential clinical implications of these results, assuming the lower doses of PTU usually employed exert a similar effect. The first concerns the possibility that PTU would be more effective than MMI in the therapy of hyperthyroidism because of its ability to inhibit extrathyroidal T_4 to T_3 conversion. It has recently been reported that serum T_3 concentrations fell more rapidly in two groups of hyperthyroid patients treated with PTU than in two other groups treated with MMI (one group receiving each agent also received iodide) (21). Differences in rates of clinical improvement were not sought in that study, and it was of only 5 days duration. However, it seems reasonable to conclude that clinical improvement might be somewhat more rapid during PTU therapy. Clinical studies concerning this point are needed. A second clinical implication of these results concerns the use of PTU alone or with T_4 in the treatment of hyperthyroidism in pregnant women. Serum T_3 concentrations in the fetus are very low (22–25). The finding of thyroidal T_4/T_3 ratios in the fetus that are similar to those in thyroid tissue from adults suggests that the low serum T_3 concentrations in the fetus are not due to low thyroidal T_3 secretion, but rather are a consequence of poor or even absent peripheral T_4 to T_3 conversion (23). The use of PTU, which would not only inhibit fetal thyroid secretion but might also inhibit extrathyroidal conversion of T_4 to T_3, if it occurs, could be hazardous in this situation where availability of T_3 is already extremely limited. This would be the case whether the circulating fetal T_4 was produced by the fetal thyroid or reached the fetus from the mother, though there is little evidence that there is appreciable maternal to fetal transfer of T_4 (26–28).

ACKNOWLEDGMENTS

We gratefully acknowledge the skilled nursing care provided by Miss Cordelia Shute and her staff of the Clinical Research Center, the technical assistance of Mrs. Maryanne O'Neill and Miss Leona Scott, and the secretarial assistance of Mrs. Olivia Phillips.

This study was supported by U. S. Public Health Service Grants RR 40 (Clinical Research Center), 5 TO 1 AM-05649 and 5 RO 1 AM-14039.

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